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EXAMINER	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/638,358
Filing Date: August 15, 2000
Appellant(s): MOSCA, JOSEPH D.

Raymond J. Lillie

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 4/23/04.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct. Claims 19-39 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,962,320 (Robinson et al.) in view of U.S. Patent No. 5,591,625 (Gerson et al.). Please note however, that while the brief includes a summary of the examiner's position from the perspective of the appellants, the rejection of record made by the examiner is presented in full below in the section (10) entitled "Grounds of rejection".

(7) Grouping of Claims

The appellant's statement in the brief that certain claims do not stand or fall together is not agreed with because the appellant has not provided arguments as to why the instant grounds of rejection based on the teachings of Robinson et al. in view of Gerson et al. do not apply equally to the mesenchymal stem cells as broadly claimed in claim 19 and the adipocyte lineage cells as broadly claimed in claim 29. In the arguments section of the brief, the appellants simply state that there are two aspects of the invention, the mesenchymal stem cells as broadly claimed in claim 19 and the adipocyte lineage cells as broadly claimed in claim 29. However, mesenchymal stem cells constitute adipocyte lineage cells as mesenchymal stem cells differentiate into adipocytes. Therefore, in the absence of any specific argument as to why the instant grounds of rejection do not apply equally to the cells as claimed in claims 19 and 29, the office finds that the rejected claims **do** stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5,962,320	ROBINSON et al.	10-1999
5,591,625	GERSON et al.	1-1997

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 19-39 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,962,320 (10/5/99), hereafter referred to as Robinson et al., in view of U.S. Patent No. 5,591,625 (1/7/97), hereafter referred to as Gerson et al.. This rejection is set forth below and in prior Office actions mailed on 4/8/02, 11/4/02, and 3/19/03.

Please note that the claims on appeal are subject to an election of species requirement, see the office action mailed on 12/19/01. In the response received from the appellants dated 1/24/02, the appellants elected species a) MHC Class II, for examination on the merits. The restriction/election requirement was made final in the office action mailed on 4/8/02. Dependant claims 20-21, and 31-32 are limited to the elected subject

matter. Claims 19, 22-30, and 33-39, however, are still generic and have not been amended to reflect the elected subject matter. All pending claims, including generic claims 19, 22-30, and 33-39, have been examined **only** to the extent that they read on the elected subject matter.

The broadest claims on appeal recite a composition comprising mesenchymal stem cells that express a co-stimulatory molecule and have been modified to have an exogenous antigen fragment bound to MHC class II , MHC class I, or CD1 such that said antigen is presented to initiate an immune response (claim 19), and a composition comprising a cell of the adipocyte lineage that expresses a co-stimulatory molecule and has been modified to have an exogenous antigen fragment bound to a primary surface molecule such that said antigen is presented to initiate an immune response (claim 29). Claims dependent on claims 19 or 29 further recite said compositions wherein the costimulatory molecule is present in an expression vector, wherein the costimulatory molecule is B7-1 or B7-2, wherein the cells are modified to have an exogenous antigen by either contacting the cell with the antigen, or by modifying the cells to contain an expression vector encoding said antigen, or wherein the cells contain a exogenous genetic material encoding interferon-gamma. As noted above, dependent claims 20-21 and 31-32 recite the limitation wherein the exogenous antigen is bound to MHC II, and thus reflect the species election.

Robinson et al. teaches methods of making engineered antigen presenting cells (APCs) by transfecting cells that are not professional antigen presenting cells with a vector encoding a co-stimulatory molecule such as B7-1 or B7-2 (Robinson et al., columns 21-24, claims 1-26). Robinson et al. further teaches the use of non-professional

antigen presenting cells transfected with a nucleic acid encoding a co-stimulatory molecule and further transfected with a nucleic acid encoding an antigen and an MHC class II molecule for the stimulation of immune responses both *in vitro* and *in vivo* (Robinson et al., columns 7-9). Robinson et al. also teaches that the engineered APCs can be pulsed with exogenous antigen rather than transfected with a nucleic acid encoding the exogenous antigen in order to stimulate T cells (Robinson et al., columns 7-8). In addition, Robinson et al. teaches that the engineered APCs can further be modified to express interferon-gamma (Robinson et al., columns 7-9). It is also noted that Robinson et al. teaches that cells useful for preparing engineered APCs can be obtained from such sources as the ATCC Catalogue of Cell Lines & Hybridomas, or isolated from any tissue using known separation methods (Robinson et al., column 9, lines 66-67, and column 10, lines 1-24).

Robinson et al. differs from the instant invention in that Robinson et al., while teaching that any primary non-professional antigen presenting cell or non-professional APC cell line can be modified to express a co-stimulatory molecule and an antigen that binds MHC class II, does not specifically teach the use of mesenchymal stem cells or cells of the adipocyte lineage in general. Gerson et al. supplements Robinson et al. by teaching purified human mesenchymal stem cells useful as host cells for the expression of exogenous gene products (Gerson et al., column 1, and column 18, claim 1). Gerson et al. further teaches that the mesenchymal stem cells can be transduced or transfected with a therapeutic gene and administered to a host for treatment of disease (Gerson et al., columns 1-2). Gerson et al. further provides motivation for using mesenchymal stem cells over other cell types by teaching that the advantages of transduced mesenchymal stem

cells include the ability to express newly introduced genes in the stem cells and their progeny in a less restrictive fashion than other cells, thereby expanding the potential application in treating medical disease (Gerson et al., column 3, lines 12-24). Thus, based on the motivation provided by Gerson to use transduced human mesenchymal stem cells for *in vivo* therapy, and the teachings of Robinson et al. that any primary non-professional antigen presenting cells can be engineered to induce immune responses, it would have been *prima facie* obvious to the skilled artisan at the time of filing to use human mesenchymal stem cells as the primary non-professional antigen presenting cell in the methods of making and using engineered APCs taught by Robinson et al. Further, in view of the teachings of Gerson et al. regarding the isolation, culturing, and genetic manipulation of mesenchymal stem cells, and the high level of skill in molecular biology at the time of filing, the skilled artisan would have had a reasonable expectation of success in transfecting a mesenchymal stem cell with a vector encoding B7-1 or B7-2, and further modifying the cell to present an antigen bound to MHC class II.

(11) Response to Argument

Appellant's arguments have been fully considered but have not been found persuasive in overcoming the grounds of rejection for reasons discussed in detail in previous office action and presented in full below.

The appellant argues that Robinson et al. does not teach or suggest modifying a mesenchymal stem cell or a cell of the adipocyte lineage to express at least one co-stimulatory molecule and to have at least one exogenous antigen fragment bound to a

surface molecule. As such, the appellant argues that Robinson et al. does not render the invention as claimed obvious. The appellant further argues that although Gerson teaches genetic engineering of mesenchymal stem cells to express various therapeutic agents, does not teach mesenchymal stem cells that express at least one co-stimulatory molecule and that have at least one exogenous antigen fragment bound to a surface molecule. As such, the appellant argues that Gerson et al. does not render the instant invention as claimed obvious.

In response to applicant's arguments against the references individually, the appellant is reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The instant rejection is not based solely on the teachings of Robinson et al. or solely on the teachings of Gerson et al. The rejection of record is based on the combined teachings of Robinson et al. in view of Gerson et al.

The appellant further argues that the combined teachings of Robinson et al. in view of Gerson et al. do not suggest the instant invention as claimed, and that the office has applied an improper "obvious to try" rationale as the basis for obviousness, citing *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, *American Hospital Supply Corp. v. Travenol Laboratories, Inc.*, and *In Re Dow Chemical*.

In response to appellant's argument that there is no suggestion to combine the references, the Office recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references

themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The appellant is further reminded that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988). In the instant case, the office recognizes that neither of Robinson et al. nor Gerson et al. alone teach all the limitations of the claimed invention. However, the office has provided motivation to combine the teachings of these references to produce the claimed invention. Motivation was provided by 1) the teachings of Gerson et al that the advantages of transduced mesenchymal stem cells over other type of cells include the ability to express newly introduced genes in the stem cells and their progeny in a less restrictive fashion than other cells, thereby expanding the potential application in treating medical disease (Gerson et al., column 3, lines 12-24), and 2) the teachings of Robinson et al. that any primary non-professional antigen presenting cells can be engineered to induce immune responses (Gerson et al., columns 9-10). Please note that the fact that Robinson et al. does not specifically recite mesenchymal stem cells in the partial list of cells provided in column 9, lines 31-45, does not detract from the central teachings of Robinson et al. that any primary cell or cell line can be engineered to become a professional antigen presenting cell using their disclosed methods. In fact, the very diversity of the cells listed in column 9 demonstrates that the type of cell used to

produced the engineered APC taught by Robinson et al. is not crucial. Therefore, as stated in the rejection of record, based on the motivation provided by Gerson to use transduced human mesenchymal stem cells for in vivo therapy, and the teachings of Robinson et al. that any primary non-professional antigen presenting cells can be engineered to induce immune responses, it would have been *prima facie* obvious to the skilled artisan to use human mesenchymal stem cells as the primary non-professional antigen presenting cell in the methods of making engineered APCs taught by Robinson et al. Further, in view of the teachings of Gerson et al. regarding the isolation, culturing, and genetic manipulation of mesenchymal stem cells, and the high level of skill in molecular biology at the time of filing, the skilled artisan would have had a reasonable expectation of success in transfecting a mesenchymal stem cell with a vector encoding B7-1 or B7-2, and further modifying the cell to present an antigen bound to MHC class II.

In regards to appellant's argument that an improper "obvious to try" rationale was applied, please note that the office has properly applied the standard for obviousness set for in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) and provided specific motivation for combining the teachings of Robinson et al. and Gerson et al. to produce the claimed invention based on the desirability of using genetically modified mesenchymal stem cells over other cell types as taught by Gerson et al. and the clear teachings of Robinson et al. that any type of primary cell or cell line can be made into an engineered antigen presenting cell by genetically modifying the cell to express a co-stimulatory molecule, an antigen, and MHC II. Thus, having applied the proper standard for obviousness, the office maintains that the claims as written are *prima facie* obvious in view of the combined teachings of Robinson et al. and Gerson et al.

For the above reasons, it is believed that the rejection should be sustained.

Respectfully submitted,

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July 7, 2004

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